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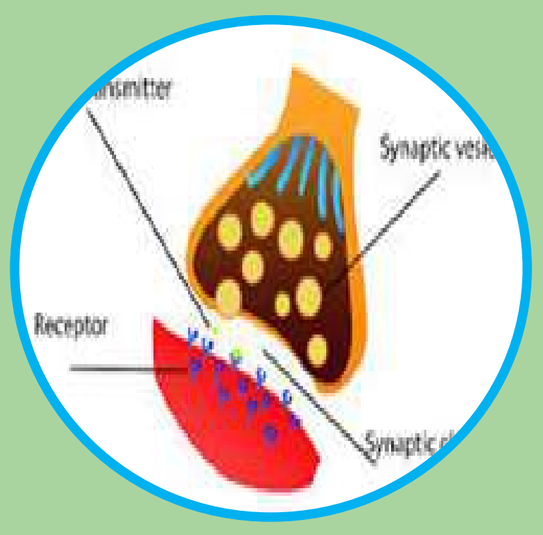

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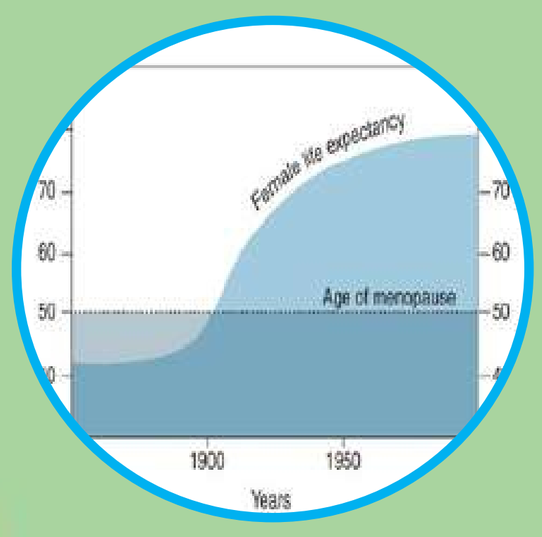

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GENERAL

PROBIOTICS AND THEIR UTILITY

SANJAY AGRAWAL , REENA DHARMESH MEHTA

Introduction:

In 2001, the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO) defined probiotics as live microorganisms which, if administered in an adequate amount, confer a health benefit to the host. This definition was maintained by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2013.

The term probiotic can be subcategorized to include probiotic drugs, probiotic foods (e.g., foods, food ingredients, and dietary supplements), direct-fed microbials (probiotics for animal use), and designer probiotics (genetically modified probiotics)[1]

In the United States, probiotics are considered to be foods or biologics, depending on their intended use. Regardless of how a probiotic is currently marketed, when it is intended to prevent or treat a disease or abnormal condition, it becomes a □drug.□ According to an FDA working definition, probiotics are classified as □live biotherapeutics□: □live microorganisms with an intended therapeutic effect in humans, including bacteria and yeast used in disease prevention or treatment, intended local or regional action.□ It includes □probiotics for clinical use[2]□

New species and more specific strains of bacteria are constantly being sought for development of novel probiotic products. The incorporation of novel bacterial strains into foods and therapeutic products requires reconsideration of the procedures for safety assessment and their safety cannot be assumed. **Probiotic products which claim specific nutritional, functional or therapeutic characteristics blur the boundaries between food, dietary supplement or medicine and both their efficacy and safety should be carefully assessed.**

Probiotics : Regulatory Status

Depending on the intended use of a probiotic, whether as a drug or a dietary supplement, regulatory requirements differ. According to the Food and Drug Administration(FDA) definition, a drug is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

If a probiotic is intended for use as a drug, then it must undergo the regulatory process as a drug, which is similar to that of any new therapeutic agent. An Investigational New Drug application must be submitted and authorized by FDA before an investigational or biological product can be administered to humans. The probiotics drug must be proven safe and effective for its intended use before marketing.

If a probiotic is intended for use as a dietary supplement, it is placed under the umbrella of □foods,□ and as such is regulated by FDA□s Center for Food Safety and Applied Nutrition. A dietary supplement is defined by the Dietary Supplement Health and Education Act (DSHEA) of 1994 as a product taken by mouth that contains a □dietary ingredient□ intended to supplement the diet. Supplements must contain >1 of the following dietary ingredients:a vitamin; a mineral; an herb or other botanical (excluding tobacco); an amino acid; a dietary substance for use by persons to supplement the diet by increasing the total dietary intake; a concentrate, metabolite, constituent, extract; or combination of any of the above . Also, since implementation of the Dietary Supplement and Non-prescription Drug Consumer Protection Act in 2006, manufacturers and distributors of dietary supplements have been required to record and forward to FDA any directly received reports of serious adverse events associated with use of their products.

In contrast to drugs, dietary supplements do not need FDA approval before being marketed. However, manufacturers need to notify FDA before marketing a product. According to DSHEA, the manufacturer is responsible for determining that the dietary supplements that it manufactures or distributes are safe and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading; the manufacturers need not provide FDA with evidence that substantiates the safety or purported benefits of their products, either before or after marketing.

In Australia, probiotics marketed for specific health benefits require premarket review by the Therapeutic Goods Administration and are usually regulated as complementary

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medicines. In Japan, those probiotic products marketed for a specified health use also require formal premarket review by the Health Ministry.

Probiotic Safety: Existing guidelines

In recent years several organisations have formulated approaches to assess the safety of probiotics. The Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food, proposed a framework consisting of strain identification and functional characterisation, followed by safety assessment and Phase 1, 2 and 3 human trials. It recommended that probiotic foods be properly labelled with the strain designation, minimum numbers of viable bacteria at the end of shelf-life, storage conditions and manufacturer□s contact details.

The Working Group suggested the following minimum tests to ensure safety:

- □ Determination of antibiotic resistance patterns
- □ Assessment of metabolic activities (e.g. D-lactate production, bile salt deconjugation)
- □ Assessment of side-effects during human studies.
- □ Post-market epidemiological surveillance of adverse incidents in consumers.
- □ If the strain being evaluated belongs to a species known to be either a mammalian toxin producer or to have haemolytic potential; it must be tested for toxin production or haemolytic activity.

The European Food Safety Authority (EFSA) has proposed a scheme based on the concept of Qualified Presumption of Safety (QPS)[3].

Broadly the characteristics to be evaluated for QPS approval are:

- □Unambiguous identification at the claimed taxonomic level.
- □Relationship of taxonomic identity to existing or historic nomenclature.
- □Degree of familiarity with organism, based on weight of evidence.
- □Potential for pathogenicity to humans and animals and

The end use of the micro-organism.

The Center for Biologics Evaluation and Research (CBER), which regulates human biologics, recommends that safety studies also assess the antibiotic susceptibility of the strain, adherence, colonization, pathogen binding inhibition, duration of fecal shedding, potential translocation across the gut lumen under certain circumstances, and adequate attenuation, inactivation, and/or control for reversion to toxicity or virulence .

Since development of these guidelines, only a few manufacturers have conducted small, randomized, controlled studies in humans to prove efficacy and safety of their products. More manufacturers should take on the responsibility of providing information to consumers and clinicians about the type and extent of safety assessments that have been conducted on their products.

Probiotics: Potential Risks

Probiotics are often regulated as dietary supplements rather than as pharmaceuticals or biological products. Thus, there is usually no requirement to demonstrate safety, purity, or potency before marketing probiotics. The safety of a commercially available probiotic product depends not only on the probiotic organism but on the other constituents of the product, be it a food or medicinal formulation.

As live microbial products, probiotics have several potential sources of risk as mentioned below[4]

(1) Intrinsic toxicity (e.g., a dangerous bacterium),

(2) Intrinsic variation (e.g., virulent variants of the same bacterial species),

(3) Product misidentification,

(4) Product mislabeling,

(5) Contamination, and

(6) Adulteration

Probiotics may be responsible for four types of side effects in susceptible individuals: systemic infections, harmful metabolic activities, excessive immune stimulation, and gene transfer.[5]

Infection

The most important area of concern with probiotic use is the risk of sepsis. One theoretical concern with the safety of probiotics is that some have been designed or chosen to have good adherence to the intestinal mucosa, and this is considered important for their mechanism of action. Adherence to the intestinal mucosa may also increase bacterial translocation and virulence. The most potent probiotics, therefore, may have increased pathogenicity.The relation between mucosal adhesion and pathogenicity in Lactobacillus spp. is supported by the finding that blood culture isolates of Lactobacillus spp. adhere to intestinal mucosa in greater numbers than do isolates from human feces or dairy products[6].

Patients with any of the following risk factors are at increased risk of developing sepsis following use of probiotics:

1) Immune compromise, including a debilitated state or malignancy
2) Premature infants
3) Central Venous Catheter
4) Impaired intestinal epithelial barrier, eg, diarrheal illness, intestinal inflammation
5) Administration of probiotic by jejunostomy
6) Concomitant administration of broad spectrum antibiotics to which probiotic is resistant
7) Probiotics with properties of high mucosal adhesion or known pathogenicity
8) Cardiac valvular disease (Lactobacillus probiotics only)

Deleterious metabolic activities

The GI microflora plays an important role in many metabolic activities, such as digestion of complex carbohydrates, lipid metabolism, and glucose homeostasis[7]. There is therefore a theoretical risk of adverse metabolic effects from manipulation of the microflora with the use of probiotics. The likelihood of significant adverse effects in this regard seems low as probiotic studies to date have not shown significant adverse effects on growth or nutrition[8]

Immune deviation or excessive immune stimulation

The GI microflora plays an important role in a range of immune functions, including antibody production, the development and persistence of oral tolerance to food antigens, and the formation of germinal centres within lymphoid follicles[9]. This crucial role of the GI micoflora in normal immune development suggests that manipulations designed to alter the microflora may have significant immunomodulatory effects. The long-term effects of these manipulations on the host is difficult to predict, and adverse effects on immune development remain a possibility. This is particularly relevant with use of probiotics in neonates and in pregnant women.

Gene Transfer

Whether resistance genes can be transferred by a probiotics organism to the endogenous flora, or vice versa, and the impact this would have on antibiotic treatment has yet to be elucidated.

Lactic acid bacteria are naturally resistant to many antibiotics by virtue of their structure or physiology. In most cases the resistance is not transferable. However, it is possible for plasmid-associated antibiotic resistance to spread to other species and genera. Studies with lactic acid bacteria, have demonstrated presence of plasmids with antibiotic-resistance genes, including genes encoding resistance to tetracycline, erythromycin and chloramphenicol. These resistance plasmids have been found in *L. reuteri, L. fermentum, L. acidophilus, and L. plantarumin* raw meat, silage, and feces of animals[10].

Even though probiotics colonize the human intestine transiently, concern exists regarding the possible transfer of antimicrobial resistance from probiotic strains to more pathogenic bacteria in the intestinal microbiota. Many *Lactobacillus* strains are naturally resistant to vancomycin, which raises concerns regarding the possible transfer of such resistance to more pathogenic organisms, particularly enterococci and *Staphylococcus aureus.*

Safety of Probiotics: Review of Current Evidence

Despite increasing scientific interest in probiotics and their widespread and growing use, very few properly conducted clinical trials have studied their short-term and long-term safety.

Majority of the published clinical trials conducted with probiotics have included small number of patients per trial, have used a variety of probiotic strains and wide range of daily doses, and even the duration of administration among different trials is highly variable. This makes proper assessment of efficacy and safety of probiotics difficult.

In 2011, a report was released by the Agency for Healthcare Research and Quality (AHRQ) based on research sponsored by the National Institutes of Health and the FDA and conducted by the Southern California Evidence-based Practice Centre reviewing the safety of probiotics. The report was an exhaustive review of the literature including 622 studies of organisms from 6 genera: Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, and Bacillus. The authors of the report concluded that, the vast majority of the existing published studies simply have not adequately assessed and reported on safety of probiotics. Even when assessments are made, these are inconsistent[11].

The most commonly reported side effects of probiotics from short-term studies are related to the gastro-intestinal tract. These side effects include: abnormal bowel movements, bloating, flatulence, gurgling, and stomach aches.

A systematic review of original articles published between 1976 and 2018 was carried out to study infectious complications related to probiotic ingestion.[12] A search of PubMed, SciELO and Scopus databases revealed 60 case reports and 7 case series, making up a total of 93 patients. The results of this systemic review are summarised below:

Occurrence of infectious complications:

Fungemia was most commonly observed complication. There were 35 (37.6%) cases of fungemia. Sepsis was identified in 29 (31.2%) patients and bacteraemia was reported in 19 (20.4%) of cases. This was followed by endocarditis and abscess, with 4 and 3 cases, respectively. Pneumonia, pleural empyema and septic arthritis were present in only one case each.

Probiotic microorganisms involved in infectious complications:

Saccharomyces spp.

Among the 93 cases, 47 (50.5%) were due to Saccharomyces. In 5 patients, Saccharomyces boulardii (S. *boulardii*) was isolated from blood, in 41 cases S.*cerevisiae* was isolated from biological samples and in only one case the species was not identified. In 27 cases, the probiotic microorganisms in the medications were compatible with the isolates found in the blood samples of the patient.

Lactobacillus spp.

Lactobacillus spp. were the etiologic agents in 26 episodes

of infectious complications after probiotics use; 14 were identified as L. *rhamnosus*, 4 as L. acidophilus,3 as L. *paracasei,* 1 as L. *casei* and 4 cases were not identified at species level

Bifidobacterium spp.

Of the 12 patients with infectious complications due to Bifidobacterium spp., 10 were newborns (9 preterm). B. *longum* was present in 6 cases of infectious complications, followed by B. *infantis* and B. *breve*, with two cases each.

Bacillus spp.

One case series described 4 cases of bacteremia caused by B. subtilis associated with the use of probiotics containing these microorganisms; the probiotic was given to reduce the number of diarrheal episodes related to enteral nutrition.

Probiotics: At Risk Population

Although most commercially available probiotic strains are widely regarded as safe, there are significant concerns with respect to safety in particular populations.

According to the FDA following populations are potentially at risk for adverse events with use of probiotics:

1. **Immunosuppressed-**

   anti-rejection medication after stem cell or solid organ transplant, injectable immunosuppressive drugs for autoimmune disease, or corticosteroids (greater than ½ mg per kg body weight or prednisone or its equivalent);chemotherapy or radiation

2. **Structural heart disease-**

   Valve abnormality or replacement, history of endocarditis

3. **Potential for translocation of probiotic across bowel wall-**

   Presence of an active bowel leak, acute abdomen, active intestinal disease including colitis, or significant bowel dysfunction; presence of neutropenia or anticipation of neutropenia after chemotherapy; radiation therapy

4. **Pregnant women**

Probiotics: Way Forward

To monitor the safety of probiotics, it is important to conduct population-based surveillance for the isolation of probiotic bacteria from patients with infection. There should be knowledge of the susceptibility profile for any strain used in clinical trials[13] and facilities to compare the clinically isolated strain with the probiotic strain by use of molecular methods should be readily available. Any trial using a probiotic strain should have active surveillance for cases of infection associated with such use and for the occurrence of other adverse effects.

For greater acceptance and judicious use of probiotics, following information should be generated for each probiotic product:

- Identification and characterization of the probiotic strains
- Its mechanisms of action should be elucidated with proper scientific studies
- Its Clinical effectiveness should be established by properly designed, randomized, blinded, placebo-controlled clinical trials
- The relationship between the dose and duration of probiotic therapy and its clinical effects, on a strain by strain basis should be well documented
- Short-term and long-term safety of probiotic strains
- Risk-benefit analysis : The risks and benefits of probiotic therapy should be compared with existing treatments options
- Accurate labelling and proper storage

Safety of Probiotics: Summary

In view of the increasing use of probiotics as health supplements and therapeutic agents, clinicians need to be aware of the risks and benefits associated with their use.

The use of probiotics cannot be considered risk-free and their safety should be carefully evaluated, as use of probiotics is known to cause bacteremia, fungemia and sepsis in immunocompromised individuals. Vigilant reporting of adverse events resulting from probiotic use is necessary to establish the safety profile of these agents when they are used in other than healthy populations. Physicians caring for immunocompromised or critically ill patients must be fully aware of these potential serious complications of probiotic use.

Better designed studies are needed to answer questions related to effectiveness and safety of probiotics. Proper risk-benefit analysis of probiotics should be carried out to study their potential for the prevention and treatment of various critical illnesses[14].

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